REMARKS

This is in response to the Office Action dated October 27, 2009. After entry of this amendment, claims 1-15 are pending. Claim 1 has been amended without prejudice or disclaimer and find support *inter alia* in the original claim. No new matter has been added.

Rejections under 35 U.S.C. 103(a)

Claims 1-11 and 13-15 are rejected under 35 U.S.C. §103(a) as being obvious over Wilms *et al.* (hereinafter "Wilms") in view of Moralejo *et al.* (hereinafter "Moralejo"). Applicants respectfully traverse and urge reconsideration of the rejection for the reasons of record and for the following additional reasons.

The Examiner characterizes Wilms as allegedly teaching host cells having the L-rhamnulose kinase (RhaB) gene inactivated which would reduce consumption of the expensive inducer L-rhamnose when the cells are used to produce a heterelogous polypeptide enzyme. The Examiner acknowledges that Wilms does not teach inactivation of the L-rhamnose isomerase (RhaA) gene in the host cell, but relies on Moralejo for such teaching. The Examiner characterizes Moralejo as allegedly teaching the gene cluster encoding enzymes for L-rhamnose metabolism in *E. coli* and that inactivation of rhamnose isomerase would be expected to block any catabolism of L-rhamnose. The Examiner accordingly contends that one skilled in the art would have been motivated to substitute the inactivation of RhaB in the method of Wilms with the inactivation of RhaA to greatly reduce the amount of the expensive inducer L-rhamnose needed to induce the expression of a heterelogous polypeptide. Applicants respectfully disagree.

As noted by the Examiner, Wilms discloses a method for recombinantly expressing nucleic acid sequences using an expression system based on the rhamnose-inducible rha_{BAD} promoter in a rhaB defective host cell. The method taught in Wilms was characterized by the authors as being one of the most cost-effective means to enhance cell mass and protein production. See Wilms, page 101, right Col., 1st paragraph. At the time of developing their method, the gene cluster encoding the enzymes for L-rhamnose metabolism in *E. coli* was known in the art as evidenced by Moralejo. Also known in the art was the alleged suggestion made in Moralejo to block any catabolism of L-rhamnose by inactivating rhamnose isomerase. However, the authors of Wilms deliberately chose inactivating the rhaB gene of the host cell for their

method. According to their own characterization, the rhaB gene was chosen for inactivation because the phosphorylation of L-rhamnulose (catalyzed by rhamnulose kinase encoded by the rhaB gene) is the first irreversible step in the degradation of L-rhamnose to dihydroxyacetone phosphate and L-lactaldehyde. Wilms, page 98, left Col., lines 4-8. As discussed in the Discussion section at pages 101-102, various factors may affect the specific productivity of a cell. Thus, any changes to an established expression system, including substituting rhaB-defective host cell with rhaA-defective host cell as suggested by the Examiner, would likely affect the specific productivity of a cell. Thus, one skilled in the art, upon reading Wilms, would not have simply modified the method taught therein by using a host cell that is defective in a different gene with a reasonable expectation of success that the productivity of the cell would be maintained. For at least the above reasons, Wilms is actually teaching away from using a host cell that is defective in genes other than the rhaB gene. Accordingly, Wilms and Moralejo are not combinable and a *prima facie* case of obviousness has not been established.[1]

Moreover, it is noted that, depending on the cultivation conditions, different concentration of inducer (i.e. L-rhamnose) is required for induction of the rha_{BAD} promoter in the method taught in Wilms. For instance, in shake-flask experiments, 0.1 g/L of L-rhamnose is allegedly sufficient for induction of the rha_{BAD} promoter. See Wilms at page 100, left Col., lines 1-3 of the 2nd paragraph. In high-cell-density fermentation such as production in a fermenter, however, higher concentration of L-rhamnose is needed for effective induction of the promoter. See Wilms at page 100, left Col., 2nd paragraph, and Figure 6. As described therein and demonstrated in Figure 6, at a concentration of 0.5 g/L, the rhamnose was almost completely taken up from the cells but the enzymatic activity produced by the induction of the rha_{BAD} promoter was only about half of the activity obtained in shake-flask experiments. See Wilms at page 100, left Col., 2nd paragraph. It is thus clear that the concentration of 0.5 g/L of L-rhamnose was not sufficient for effective induction of the rha_{BAD} promoter in high-cell-density fermentation. As also described therein, a concentration of 2 g/L of L-rhamnose seems to be

[1] It is well established that under 35 U.S.C. § 103 the Examiner must consider the reference in its entirety, *i.e.* as a whole, including portions that teach away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); see also *KSR*, 127 S. Ct. at 1740; MPEP § 2141.03 (VI). It is improper to combine references where the references teach away from their combination. *See* MPEP § 2145 (X)(D)(2) (citing *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

optimal for effective induction of the rha_{BAD} promoter in high-cell-density fermentation conditions. Thus, the problem to be solved in Wilms is how to achieve an effective production comparable to that obtained in shake-flask experiments in high-cell-density fermentation conditions such as production in a fermenter while uses only low concentration of inducer. Neither Wilms nor the art provides any suggestion as to how to solve this problem. Further, because the expression system using the rhaB-defective host cell taught in Wilms produces effective production in shake-flask experiments, one skilled in the art, upon reading Wilms, would have been motivated to search for any differences between the two different cultivation conditions (i.e. shake-flask and high-cell-density fermentation) and make necessary modifications accordingly in order to solve such a problem. As such, a skilled artisan would not have expected that the problem can be attributed to the use of the rhaB-defective host cell and thus, would not have been motivated to consult with the rhamnose operon described in Moralejo and substitute the rhaB-defective host cell with a host cell that is deficient in a different gene such as the rhaA gene. Accordingly, Wilms and Moralejo are not combinable for this additional reason and thus, the cited references do not render the claimed method obvious.[2]

Because Wilms teaches away from using a host cell that is defective in genes other than the rhaB gene, and because Wilms and Moralejo are not combinable, a *prima facie* case of obviousness has not been established. For the reasons of record and for at least the above additional reasons, reconsideration and withdrawal of the rejection is respectfully requested.

Claim 12 is rejected under 35 U.S.C. §103(a) as being obvious over Wilms in view of Moralejo, and further in view of Israelsen et al. (hereinafter "Israelsen"). Applicants respectfully disagree.

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[2] It is well established that under 35 U.S.C. § 103 the Examiner cannot selectively pick and choose from the disclosed parameters without proper motivation as to a particular selection. The mere fact that a reference may be modified to reflect features of the claimed invention does not make the modification, and hence the claimed invention, obvious ***unless the prior art suggested the desirability of such modification***. *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992) (emphasis added). "[R]ejections on ***obviousness cannot be sustained by mere conclusory statements***; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness . . . a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art . . . it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements ***in the way the claimed new invention does***." *See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) (emphasis added). Thus, it is impermissible to simply engage in a hindsight reconstruction of the claimed invention where the reference itself provides no teaching as to why the applicant's combination would have been obvious. *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

As discussed above, Wilms and Moralejo, alone or in combination, do not render the main claim obvious. Since claim 12 depends from claim 1, the cited references, Wilms and Moralejo, further in view of Israelsen, would not render claim 12 obvious for essentially the same reasons as detailed above. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

For at least the above reasons, Applicants respectfully request withdrawal of the rejections and allowance of the claims. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number given below.

This response is filed within the three-month period for response from the mailing of the Office Communication, to and including October 27, 2009. No fee is believed due. However, if a fee is due, the Director is authorized to charge our Deposit Account No. 03-2775, under Order No. 12810-00091-US from which the undersigned is authorized to draw.

Respectfully submitted,

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